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SYSTEMATIC REVIEW

Effect of Aidi injection plus chemotherapy on gastric carcinoma: a Meta-analysis of randomized controlled trials

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Abstract

OBJECTIVE: To conduct a Meta-analysis of studies on the effect of Aidi injectioncombined with chemotherapy versus chemotherapy alone in the treatment of gastric cancer (GC).

METHODS: Nine electronic databases and six gray literature databases were comprehensively searcheduntil April 20, 2013. Two reviewers independently selected and assessed included trialsaccording to the inclusion and exclusion criteria. The risk of bias tool from the Cochrane Handbook version 5.1.0 was used to assess trial quality. All calculations were performed using Review Manager 5.0.

RESULTS: Thirty-two studies including 1927 participants met the inclusion criteria, most of which were low quality. Compared with chemotherapy alone, Aidi injection plusthe same chemotherapy significantly improved the effective rate [*OR* = 1.52, 95% *CI* (1.24, 1.86), *P* < 0.0001], clinical beneficial rate [*OR* = 1.77, 95% *CI* (1.33, 2.36), *P* < 0.0001], and quality of life [*OR* = 3.02, 95% *CI* (2.39, 3.82), *P* < 0.000 01]. There was a significant improvement in nausea and vomiting incidence [*OR* = 0.34, 95% *CI* (0.24, 0.47), *P* < 0.000 01], diarrhea [*OR* = 0.47, 95% *CI* (0.33, 0.69), *P* < 0.000 01], leukopenia (Ⅲ-Ⅳ) [*OR* = 0.34, 95% *CI* (0.23, 0.51), *P* = 0.05], hemoglobin decrease (Ⅲ-Ⅳ) [*OR* = 0.42, 95% *CI* (0.18-1.00), *P* = 0.05], thrombocytopenia (Ⅲ-Ⅳ) [*OR* = 0.46, 95% *CI* (0.22, 0.96), *P* = 0.04], and damage to liver function [*OR* = 0.36, 95%*CI* (0.24, 0.54), *P* < 0.000 01].

CONCLUSION: Aidi injection combined with chemotherapy significantly improved the clinical effect of chemotherapy, reducing the incidence of adverse events. Use of the CONSORT statement for randomized controlled trials is recommended for stricter reporting.

Key words: Drug therapy; Stomach neoplasms; Review; Randomized controlled trial; Aidi injection

INTRODUCTION

Gastric carcinoma (GC) is one of the common malignant carcinomas. GC is the fourth most frequent malignant cancer and the second most common cause of death, with an incidence of 989 600 cases and 738 000 deaths worldwide in 2008.[1] More than 70% of new cases and deaths occur in underdeveloped countries.[2] In China, there were 464 000 new gastric carcinoma cases and 352 000 deaths in 2008, accounting for 16.5% of allcancer cases and 18.0% of cancer-related deaths.[3]

Therefore, GC is a large worldwide public health burden. Surgical therapies, radiotherapies, and chemotherapies arethe three mainstays of treatment. Unfortunately, almost half of the patients that present with middle-to-advanced stage gastric cancer are inoperable, with a median survival time (MST) of 6-10 months. Therefore, comprehensive chemotherapy treatment programs aremost commonly used for GC.[4] However, chemotherapy has adverse short- and long-term side effects,[5] because the selectivity of chemotherapy is low for normal cells. Traditional Chinese medicinal herbs combined with chemotherapy could significantly improve quality of life, relieve symptoms, remove toxins, increase immune function, and act as anticancer agents.[6]

Aidi injection is made from an extraction of Renshen (*Radix Ginseng*), Huangqi (*Radix Astragali Mongolici*), Ciwujia (*Radix et Caulis Acanthopanacis Santicosi*), and Banmao (*Mylabri*).The injection can clear heat and toxins, remove blood stasis, inhibit tumor growth, induce apoptosis, decrease the side-effects of radiotherapy and chemotherapy, and increase immune function.[7,8] Aidi injection combined with chemotherapy could improve the effect of chemotherapy, increase drug tolerance, and improve quality of life.[7]

We aimed toconduct a Meta-analysis of 32 randomized controlled trials (RCTs) to assess the efficacy and safety of Aidi injection combined with chemotherapy in GC patients.

DATA AND METHODS

Study selection

The study search, study selection, data extraction, and quality assessment were performed independently by two trained reviewers (JCW and LG). Disagreements between reviewers were resolved through consensus or by consulting a third expert adjudicator (KHY).

Inclusion and exclusion criteria

Included studies met the following inclusion criteria: (a) RCTs using Aidi injection combined with chemotherapy for GC patients; (b) participants were confirmed to have GC pathologically or via computed tomography, regardless of age, sex, or nationality; (c) intervention was Aidi injection combined with chemotherapy vschemotherapy alone;and (d) relative risks (RR), odds ratios (OR), or data for calculations were provided.

Studies were excluded if: (a) the patients were not confirmed to have GC; (b) the studies were not RCTs; (c) the control measures did not include chemotherapy; (d) the data could not be extracted; or (e) the study was a review or Meta-analyses, animal study, case report, conference abstracts, or letters to journal editors.

Outcome measures

Efficiency rate was defined as complete response (CR) + partial response (PR), according to the World Health Organization (WHO)[9]criteria for solid tumors.The clinical beneficial rate was defined as complete response (CR) + partial response (PR) + stable disease (SD). Quality of life before and after treatment was assessed using the Karnofsky performance status scale (KPS), with KPS scores increasing by ≥10 points after treatment considered as improving quality of life, KPS scores decreasing by ≥ 10 points after treatment as lower quality of life, and KPS scores increasing or decreasing by < 10 points considered as stable.

According to the WHO grading criteria for acute and sub acute toxicity of anticancer drugs,[10] adverse events were evaluated after treatment,including leukopenia, thrombocytopenia, nausea/vomiting, anemia, and diarrhea. Survival time was calculated from the beginning of chemotherapy to death, withdrawal, or drop out. Immune function was measured with T lymphocyte subsets such as CD3, CD4, CD8, CD4/CD8, and NK cells before and after treatment.

Search strategy

We comprehensively searched the following databases: China Academic Journal Network Publishing Database (CAJD, 1994-2013/4), Chinese Biomedical Literature Database (CBM, 1978-2013/4), Chinese Technological Periodical Full-text Database (VIP, 1989-2013/4), China Online Journals (COJ, 1997-2013/4), Chinese Science Citation Database (CSCD, 1989-2013/4-2013/4), PubMed (1966-2013/4), EMBASE (1974-2013/4), Cochrane Library (inception-2013/4), and Science Citation Index Expanded (SCI-EXPANDED, 2000-2013/4). Grey literature was obtained from the China Proceedings of Conference Full-text Database (CPCD, 1994-2013/4), Academic Conferences in China (ACIC, 1990-2013/4), Chinese-foreign Conference Database (*via* National Science and Technology Library, 1985-2013/4), China Doctoral Dissertations full-text Database (CDFD, 1994-2013/4), China Master's Theses Full-text Database (CMFD, 1994-2013/4), and Dissertations of China (DOC, 1990-2013/4). Searches were composed of a combination of the following terms: stomach neoplasm, gastric neoplasm, stomach cancer, gastric cancer, stomach neoplasms, Aidi zhusheye, Aidi injection, Aidi, and random*. The searches were performed on April 20, 2013. The search strategy was presented as follows:

#1 Stomach Neoplasm
#2 Gastric Neoplasm
#3 Stomach Cancer
#4 Gastric Cancer
#5 Stomach Neoplasm
#6 "Stomach Neoplasms" [Mesh]
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 Aidi zhusheye
#9 Aidi injection
#10 Aidi
#11 #8 OR #9 OR #10
#12 Random*

#13 #7 AND #11 AND #12

Selection

Based on the inclusion and exclusion criteria, all searched records were classified and sorted by reference management software Endnote X6 (Thomson Reuters, New York, NY, USA), with duplicated studies discarded. Then, all abstracts were read and potentially eligible articles and citations for which a determination could not be made were gathered. The full-text versions of these articles were then obtained to determine eligibility. We contacted authors whose study reports were incomplete or lacked relevant information.

Data extraction and quality assessment

Astandardized data extraction form was designed that included basic information, the characteristics of included studies, interventions, outcome measures, and other information (Table 1).

Combined with the characteristics of TCM injection, the risk of bias tool described in the Cochrane Handbook version 5.1.0[11] and methodological section of CONSORT statement[12] were used to assess the quality of each trial (Table 1). Each item was assessed as following two responses: "complete reporting" (low risk) scored 1, while "No" or "Unclear" (high risk) scored. The total scores were 8.

Statistical analysis

Assessment of heterogeneity: we used the Chi-squared (χ^2 test to assess heterogeneity between trials and the I^2 statistic to evaluate the extent of inconsistency. If I^2 was less than 50%, and the *P*-value was greater than 0.05, then there was no statistical heterogeneity and the fixed effects model was chosen for Meta-analysis, otherwise the random effects model was used.

Data synthesis: dichotomous data were presented as an odds ratio (*OR*), and continuous outcomes by mean

Table 1 Data extraction items of included studies

Item		Interpretation
Basic information	Publication year	Year of publication of included RCT
	Source	Journal or degree paper
	Language of publication	Chinese or English
	First author	Name of first author
Characteristics	Sample size	Number of sample of included studies
	Sex	Male or women
	Age	Range/average/medium of included participants
	Pathological types of carcinoma	Early, advanced, or late GC
	Cell types of carcinoma	Adenocarcinoma, squamous carcinoma, SRCC, etc.
	Foundation item	Number and nature on foundation
	Clinical stages	Ⅱ, $Ⅲ_a$, $Ⅲ_b$, $Ⅲ_c$, Ⅳ
Interventions	Interventions	Aidi injection combine with types of chemotherapy
	Dosage	Dosage of Aidi injection
	Chemotherapies	Name and composition of chemotherapies
	Treatment cycle	Cycle of participants intervened
Outcome measures	Efficience	Name and number of efficience measures
	Security	Name and number of security measures
	Other	Name and number of other measures
	Assessment of quality of life	KPS or others
Quality assessment	Randomization	Was the trial randomized?
	Randomization method	What method was used to randomize?
	Blinding	Whether the blinding was described and performed correctly?
	Withdrawals/drop outs	As reported
	Eligibility criteria for participants	As reported
	Adverse events	Kinds of adverse events
	Statistical methods	Whether statistical methods were described?

Notes: RCT: randomized controlled trial; GC: gastric cancer; KPS: Karnofsky performance score.

difference (*MD*), with 95% confidence interval (*CI*). Forest plots were constructed to graphically present the result of outcome measures. The differences in the efficacy between interventions were considered statistically significant if $P \leq 0.05$.

Publication bias: a funnel graph was created to investigate the likelihood of overt publication bias. All calculations were performedusing RevMan software (version 5.2, RevMan software, London, England).[13]

RESULTS

Literature search

After the initial search, 124 potentially relevant publications were identified. All records were imported into EndNote X6 and 54 trials were excluded because of duplication. Among the remaining 70 trials, 38 were excluded because they were animal studies, review articles, letters, or abstracts. Finally, 32 studies were evaluated in our analysis[14-41,43-46] (Figure 1).

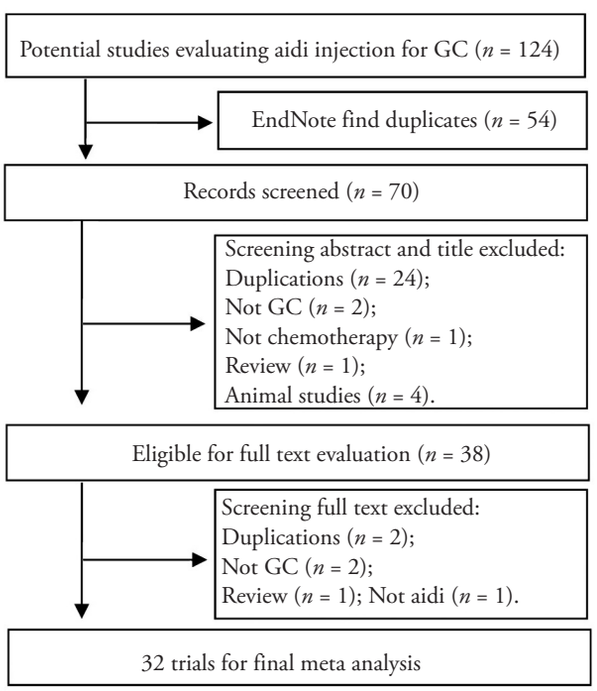

Figure 1 Flow chart of article screening and selection process

Characteristics of included trials

All 32 included studies were randomized, although no detailed descriptions were provided. Each study featured Aidi injection combined with chemotherapy as an intervention versus chemotherapy alone. Chemotherapy drugs included fluorouracil, mitomycin, oxaliplatin, cisplatin, paclitaxel, docetaxel, capecitabine, leucovorin, epirubicin, and mitomycin. A total of 1927 participants were included in the 32 studies. The median age of included participants was 60 (range: 31-108) years. All participants were confirmed to suffer from GC by pathology, computed tomography, cytology, and gastroscopy. Nineteen studies reported clinical stages, and most participants were in stages Ⅲ or Ⅳ. A clinical efficacy rate was reported in 28 studies; 20 studies reported quality of life, and 20 studies used Karnofsky performance status (KPS); 30 studies reported adverse events including nausea and vomiting, phlebitis, alopecia, bone marrow suppression, leukopenia, thrombocytopenia, and liver or kidney function damage. Six studies reported immune function (Table 2).

Quality assessment

Table 3 shows the result of quality assessment. Only two studies were found to be high quality (Score ≥ 6). The percentage that reported randomization, methods of randomization, blinding, description of blinding, withdrawals and drop outs, eligibility criteria of participants, adverse events, and statistical methods were 96.88%, 6.25%, 0%, 0%, 96.88%, 100%, 93.75%, and 93.75%, respectively.

Meta analysis results

Effective rate: twenty-eight studies[14,16,17,19-35,37-39,43-46] reported effective rate. There was no heterogeneity across the trials (P = 1.00, I^2= 0%).Therefore, the fixed-effect model was used to pool data. There was a statistically significant difference between the injection combined with chemotherapy group and the chemotherapy alone group (*OR* = 1.52, 95% *CI*: 1.24, 1.86, $P < 0.0001$), favoring the injection combined with chemotherapy group (Figure 2).

Clinical beneficial rate

Twenty-four studies[14,16,17,19-21,24-35,37-39,44-46] reported the clinical beneficial rate. There was no heterogeneity across the trials (P = 1.00, I^2= 0%).Therefore, the fixed-effects model was used to pool data.There was a statistically significant difference between the injection combined with chemotherapy group and the chemotherapy alone group [*OR* = 1.77, 95% *CI*: (1.33, 2.36), $P < 0.0001$], indicating the clinical beneficial rate of injection combined with chemotherapy was better than that of the chemotherapy alone (Figure 3).

Survival rate

One-year survival rateswere reported in six studies,[15,23,24,29,44,45] and two studies[15,45] recorded 2-year survival rates. No statistically significant heterogeneity was found (P = 0.99, I^2=0%), so we used the fixed-effects model to pool data. There was no statistically significant difference between the two groups in 1-year survival rate [*OR* = 1.51, 95% *CI*: (0.98, 2.34), P = 0.06] or 2-year survival rate [(*OR* = 1.57, 95% *CI*: (0.61, 4.00), P = 0.35)] (Figure 4).

Quality of life

Twenty studies[17,19-21,23,24,26,27,29-31,33-36,39,41,43-45] used KPS to evaluate quality of life. There was no heterogeneity across the trials (P = 0.79, I^2= 0%), so the fixed-effects model was used to pool data. Compared with chemo-

Table 2 Basic characteristics of included 32 studies

Study	Sample		Sex (man/women)		Age		Intervention		Dosages/mL	Outcome	KPS	Duration
	A+C	C	A+C	C	A+C	C	A+C	C				
Ge YL *et al* 2010[14]	25	25	28/22		NR		AIDI+MF/CF	MF/CF	50	①②	NR	2
Liu HZ *et al* 2012[15]	28	28	18/10	20/8	42-75/M56	35-76/M58	AIDI+SOX	SOX	60	①②	NR	4
Zhang XD *et al* 2011[16]	16	15	7/9	7/8	52-73/M56	49-75/M58	AIDI+XELOX	XELOX	50	①②③④	NR	2
Tang YH *et al* 2007[17]	34	30	34/30		32-75/M58		AIDI+DCF	DCF	60	①⑤	> 70	> 2
Zhan J *et al* 2013[18]	25	25	34/16		35-75		AIDI+XELOX	XELOX	50-100	①②	NR	NR
Ke YF *et al* 2010[19]	23	22	24/21		28-75/M49		AIDI+XELOX	XELOX	50-100	①②⑤	≥70	> 2
Ding Z *et al* 2009[20]	38	37	23/15	21/16	41-80	39-79	AIDI+HELF	HELF	100	①②⑤	≥60	6
Tian X *et al* 2004[21]	23	22	16/7	14/8	A52.4	A53.1	AIDI+FP	FP	50	①②⑤	>50	2
Wang ZL *et al* 2009[22]	30	26	19/11	17/9	35-78/A55	35-85/A57	AIDI+FAM	FAM	50	①②③⑤	NR	3
Gong NY *et al* 2006[23]	26	30	15/11	30/16	38-71/A54.2	41-69/A55.4	AIDI+TPLF	TCF	50	①②⑤	≥60	4
Zhang ML *et al* 2009[24]	53	51	39/14	34/17	61-79/M58	60-85/M71	AIDI+FP	FP	50	①②③⑤	≥60	2
Qin XY *et al* 2008[25]	30	30	42/18		38-71/M60		AIDI+ECF	ECF	50	①②	NR	2
Miao YQ *et al* 2011[26]	41	43	65/19		M62		AIDI+FOLFOX4	FOLFOX4	50-80	①②⑤	> 60	≥2
Chen NJ *et al* 2008[27]	36	34	38/32		40-68/A56.7		AIDI+FOLFOX4	FOLFOX4	50	①②	> 70	3
Lin H *et al* 2011[28]	22	24	26/20		32-75/M56		AIDI+POF	POF	100	①②	NR	> 2
Fan CM *et al* 2011[29]	23	28	15/8	18/10	37-83/M56.7	39-78/M57.8	AIDI+L-OHP	L-OHP	50	①②③⑤	≥60	≥4
Liu LH *et al* 2009[30]	30	30	16/14	18/12	M50.6	M49.6	AIDI+TPF	TPF	50	①②⑤	≥60	≥2
Chen LP *et al* 2012[31]	25	25	29/21		54-75/M62		AIDI+EOF	EOF	50	①②⑤	≥60	≥2
Zeng QB *et al* 2006[32]	23	22	30/15		M52.4		AIDI+OFL	OFL	50	①②④	NR	≥2
Huo CS *et al* 2012[33]	32	33	43/22		36-71/A48.5		AIDI+OFL	OFL	50	①②⑤	NR	2
Zhao JG *et al* 2009[34]	32	30	29/33		28-75/M49		AIDI+TX	TX	80	①②⑤	≥60	≥2
Chen YD *et al* 2012[35]	29	28	20/9	19/9	43-69/M56	42-68/M55	AIDI+FOLFOX	FOLFOX	80	①②⑤	50-80	2
Yang SM *et al* 2006[36]	54	54	41/13	43/11	43-75/A56.3	42-76/A55.6	AIDI+FAD	FAD	50-100	①②	NR	3-4
Yan HX *et al* 2012[37]	32	34	57/9		42-75/A61.7		AIDI+FOLFOX4	FOLFOX4	100	①②④	> 70	1
Jia LQ *et al* 2003[38]	23	22	30/15		32-70/A56.8		AIDI+FD	FD	50	①②④	NR	2

Table 2 Basic characteristics of included 32 studies (continuted)

Study	Sample		Sex (man/women)		Age		Interventions		Dosage/mL	Outcome	KPS	Durations
	A+C	C	A+C	C	A+C	C	A+C	C				
Han WL *et al* 2011[39]	31	30	20/11	19/11	45-70/A67.3	45-70/A66.1	AIDI+TG	TG	80	①④⑤	> 60	⩾2
Zhu XQ *et al* 2009[40]	34	33	20/14	21/12	37-73/M60	39-74/M58	AIDI+FOLFOX4	FOLFOX4	100	⑤	> 60	⩾2
Zhang AX *et al* 2009[41]	35	32	20/15	19/13	30-71/A55	32-68/A53	AIDI+FOLFOX4	FOLFOX4	50	①②	NR	3
Han SR *et al* 2009[43]	24	23	13/11	12/11	38-71/A54.2	41-69/A55.4	AIDI+TCF	TCF	80-100	①②⑤	> 60	1
Wen X *et al* 2010[44]	27	29	46/10		47-78/A60.3		AIDI+DFC	DFC	80	①②⑤	⩾60	⩾2
Wang YL *et al* 2007[45]	32	32	44/20		32-74/M48		AIDI+XELOX	XELOX	60	①②⑤	⩾70	6
Ruan FX *et al* 2012[46]	32	32	19/13	17/15	56-84/A67.6	58-83/A68.4	AIDI+Capecitabine	Capecitabine	60	①②	NR	1

Notes: A+C: Aidi injection+chemotherapy; C: chemotherapy; A: average; M: median; NR: not reported; MF/CF: fluorouracil/mitomycin; SOX: oxaliplatin+tegafur; XELOX: oxaliplatin+capecitabine; DCF: docetaxel+cisplatin; HELF: fluorouracil+leucovorin calcium+etoposide + HCPT; TP: fluorouracil+cisplatin; FAM: fluorouracil+mitomycin+adriamycin; ECF: adriamycin+cisplatin+fluorouracil; FOLFOX: oxaliplatin+fluorouracil+leucovorin calcium; POF: paclitaxel+leucovorin calcium+fluorouracil+oxaliplatin; TPF: paclitaxel+cisplatin+fluorouracil; EOF: epirubicin+fluorouracil+oxaliplatin; OFL: fluorouracil+oxaliplatin+mitomycin; TX: paclitaxel+capecitabine; FD: fluorouracil+cisplatin; TG: tegafur+gimeracil; KPS: Karnofsky performance score.

therapy alone, the injection combined with chemotherapy significantly improved the quality of life for patients [*OR* = 3.02, 95% *CI*: (2.39, 3.82), *P* < 0.000 01] (Figure 5).

Adverse events

Compared with the group using chemotherapy alone, the injection combined with chemotherapy could reduce the incidence of the following adverse events: nausea and vomiting[15,19,23-26,29-31,33,34,36,43] [*OR* = 0.34, 95% *CI*: (0.24, 0.47), I^2= 0%, *P* < 0.000 01], diarrhea[15,19,21,23,24,29,32,34,38,43,44] [*OR* = 0.47, 95% *CI*: (0.33, 0.69), I^2 = 0%, *P* < 0.00001] (Figure 6), leukopenia (Ⅲ-Ⅳ)[17,19,20,23-31,34,36,37,43] [*OR* = 0.34, 95% *CI*: (0.23, 0.51), I^2 = 0%, *P* = 0.05], hemoglobin decrease (Ⅲ-Ⅳ)[23,29,34,37] [*OR* = 0.42, 95% *CI*: (0.18, 1.00), I^2 = 0%, *P* = 0.05], thrombocytopenia (Ⅲ-Ⅳ)[19,20,23-25,27-31,34,36] [*OR* = 0.46, 95% *CI*: (0.22, 0.96, I^2 = 0%, *P* = 0.04] (Figure 7), damage to liver function[15,17,23-26,28-31,34] [*OR* = 0.36, 95% *CI*: (0.24, 0.54, I^2= 22%, *P* < 0.000 01], and damage to kidney function[17,23-25,30,31,34] [*OR* = 0.74, 95% *CI*: (0.35-1.58), I^2 = 0%, *P* = 0.448] (Figure 8).

Immune function

Six studies[17,21,23,32,37,39] reported indexes related to immune function, but one study[32] was excluded because SD valueswere not reported. There was high statistical heterogeneity across the studies (*P* < 0.000 01, I^2 = 95%), so the random-effects model was used to pool data. The injection combined with chemotherapy significantly improved CD3, CD4, CD4/CD8, and NK cells levels for patients: CD3 [*MD* = 6.50, 95% *CI*: (1.31, 11.69), *P* = 0.01], CD4 [*MD* = 6.63, 95% *CI*: (4.35, 8.92), *P* < 0.000 01], CD4/CD8 [*MD*=0.56, 95% *CI*: (0.36, 0.77), *P* < 0.000 01], and NK [*MD*= 5.23, 95% *CI*: (1.43, 9.04), *P* = 0.007] (Figure 9).

Publication bias

A funnel graph on effective rate was plotted to investigate the likelihood of overt publication bias. The funnel plot was not symmetrical, indicating the likelihood of publication bias (Figure 10).

DISCUSSION

Aidi injection was shown to have curative effects for liver cancer and lung cancer.However, a greater number of large-scale, double-blind, randomized control trials is needed for the patients of GC.[42] A previous Meta-analysis for Aidi injection combined with chemotherapy included 15 RCTs.[42] The study found that Aidi injection was beneficial in GC treatment. However, this previous study was limited because of the quality of the included RCTs, the low number of included studies, and publication bias.

This Meta-analysis included 32 RCTs to systematically and comprehensively examine the effectiveness, safety, and immune function of Aidi injection com-

Table 3 Results of quality assessment

Study	Randomization	Randomization method	Blinding	Blinding method	Withdrawal/ drop out	Eligibility criteria	Adverse event	Statistical method	Overall score
Ge YL *et al* 2010[14]	1	0	0	0	1	1	1	1	5
Liu HZ *et al* 2012[15]	1	0	0	0	1	1	1	1	5
Zhang XD *et al* 2011[16]	1	0	0	0	1	1	1	1	5
Tang YH *et al* 2007[17]	1	0	0	0	1	1	1	1	5
Zhan J *et al* 2013[18]	1	0	0	0	1	1	0	0	3
Ke YF *et al* 2010[19]	1	0	0	0	1	1	1	1	5
Ding Z *et al* 2009[20]	1	0	0	0	1	1	1	1	5
Tian X *et al* 2004[21]	1	0	0	0	1	1	1	1	5
Wang ZL *et al* 2009[22]	1	0	0	0	1	1	1	1	5
Gong NY *et al* 2006[23]	1	0	0	0	1	1	1	1	5
Zhang ML *et al* 2009[24]	1	0	0	0	0	1	1	1	4
Qin XY *et al* 2008[25]	1	0	0	0	1	1	1	1	5
Miao YQ *et al* 2011[26]	1	0	0	0	1	1	1	1	5
Chen NJ *et al* 2008[27]	1	0	0	0	1	1	1	1	5
Lin H *et al* 2011[28]	1	0	0	0	1	1	1	1	5
Fan CM *et al* 2011[29]	1	1	0	0	1	1	1	1	6
Liu LH *et al* 2009[30]	1	1	0	0	1	1	1	1	6
Chen LP *et al* 2012[31]	1	0	0	0	1	1	1	1	5
Zeng QB *et al* 2006[32]	1	0	0	0	1	1	1	1	5
Huo CS *et al* 2012[33]	1	0	0	0	1	1	1	1	5
Zhao JG *et al* 2009[34]	1	0	0	0	1	1	1	1	5
Chen YD *et al* 2012[35]	1	0	0	0	1	1	1	1	5
Yang SM *et al* 2006[36]	1	0	0	0	1	1	1	1	5
Yan HX *et al* 2012[37]	1	0	0	0	1	1	1	1	5
Jia LQ *et al* 2003[38]	1	0	0	0	1	1	1	1	5
Han WL *et al* 2011[39]	1	0	0	0	1	1	1	1	5
Zhu XQ *et al* 2009[40]	1	0	0	0	1	1	0	1	4
Zhang AX *et al* 2009[41]	1	0	0	0	1	1	1	0	4
Han SR *et al* 2009[43]	1	0	0	0	1	1	1	1	5
Wen X *et al* 2010[44]	1	0	0	0	1	1	1	1	5
Wang YL *et al* 2007[45]	1	0	0	0	1	1	1	1	5
Ruan FX *et al* 2012[46]	1	0	0	0	1	1	1	1	5

Study or Subgroup	Aidi+chemotherapy Events	Total	Chemotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ge YL2010 [14]	17	25	15	25	3.2%	1.42 [0.44, 4.52]
Zhang XD 2011[16]	7	16	6	15	2.3%	1.17 [0.28, 4.87]
Tang YH 2007[17]	18	34	13	30	4.3%	1.47 [0.55, 3.95]
Ke YF 2010[19]	13	23	8	22	2.3%	2.27 [0.69, 7.54]
Ding Z 2009[20]	25	38	16	37	3.7%	2.52 [0.99, 6.42]
Tian X 2004[21]	10	23	9	22	3.4%	1.11 [0.34, 3.63]
Wang ZL 2009[22]	19	30	14	26	3.6%	1.48 [0.51, 4.32]
Gong NY 2006[23]	16	26	10	30	2.4%	3.20 [1.07, 9.57]
Zhang ML 2009[24]	23	53	18	51	6.8%	1.41 [0.64, 3.10]
Qin XY 2008[25]	16	30	15	30	4.6%	1.14 [0.41, 3.15]
Miao YQ 2011[26]	24	41	23	43	6.1%	1.23 [0.52, 2.91]
Chen NJ 2008[27]	15	36	11	34	4.3%	1.49 [0.56, 3.97]
Lin H 2011[28]	13	22	7	24	1.8%	3.51 [1.03, 11.92]
Fan CM 2011[29]	11	23	10	28	3.1%	1.65 [0.54, 5.09]
Liu LH 2009[30]	16	30	16	30	4.9%	1.00 [0.36, 2.76]
Chen LP 2012[31]	13	25	10	25	3.2%	1.63 [0.53, 4.98]
Zeng QB 2006[32]	10	23	9	22	3.4%	1.11 [0.34, 3.63]
Huo CS 2012[33]	12	32	13	33	5.3%	0.92 [0.34, 2.51]
Zhao JG 2009[34]	17	32	12	30	3.8%	1.70 [0.62, 4.66]
Chen YD 2012[35]	12	29	11	28	4.3%	1.09 [0.38, 3.15]
Yan HX 2012[37]	12	32	9	34	3.6%	1.67 [0.59, 4.74]
Jia LQ 2003[38]	10	23	9	22	3.4%	1.11 [0.34, 3.63]
Han WL 2011[39]	15	31	13	30	4.5%	1.23 [0.45, 3.36]
Han SR 2009[43]	13	24	10	23	3.1%	1.54 [0.49, 4.86]
Wen X 2010[44]	16	27	15	29	3.9%	1.36 [0.47, 3.91]
Wang YL 2007[45]	23	32	17	32	3.1%	2.25 [0.80, 6.36]
Ruan FX 2012[46]	29	32	24	32	1.5%	3.22 [0.77, 13.50]
Total (95% CI)		**792**		**787**	**100.0%**	**1.52 [1.24, 1.86]**
Total events	425		343			

Heterogeneity: Chi² = 10.60, df = 26 (P = 1.00); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)

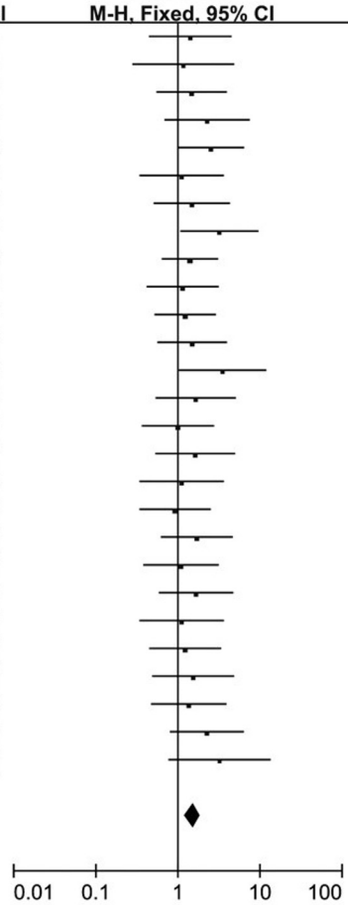

Figure 2 Effective rate Meta-analysis

Study or Subgroup	Aidi+chemotherapy Events	Total	Chemotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ge YL2010 [14]	23	25	22	25	2.5%	1.57 [0.24, 10.30]
Zhang XD 2011[16]	13	16	9	15	2.4%	2.89 [0.57, 14.68]
Tang YH 2007[17]	29	34	23	30	5.0%	1.77 [0.50, 6.29]
Ke YF 2010[19]	22	23	19	22	1.2%	3.47 [0.33, 36.24]
Ding Z 2009[20]	36	38	33	37	2.5%	2.18 [0.37, 12.71]
Tian X 2004[21]	18	23	15	22	4.7%	1.68 [0.44, 6.39]
Zhang ML 2009[24]	42	53	36	51	10.7%	1.59 [0.65, 3.90]
Qin XY 2008[25]	27	30	27	30	3.8%	1.00 [0.19, 5.40]
Miao YQ 2011[26]	40	41	41	43	1.4%	1.95 [0.17, 22.38]
Chen NJ 2008[27]	28	36	23	34	7.4%	1.67 [0.58, 4.85]
Lin H 2011[28]	18	22	15	24	3.6%	2.70 [0.69, 10.55]
Fan CM 2011[29]	20	23	24	28	4.0%	1.11 [0.22, 5.56]
Liu LH 2009[30]	27	30	28	30	3.9%	0.64 [0.10, 4.15]
Chen LP 2012[31]	23	25	22	25	2.5%	1.57 [0.24, 10.30]
Zeng QB 2006[32]	18	23	15	22	4.7%	1.68 [0.44, 6.39]
Huo CS 2012[33]	24	32	25	33	8.6%	0.96 [0.31, 2.97]
Zhao JG 2009[34]	28	32	24	30	4.3%	1.75 [0.44, 6.94]
Chen YD 2012[35]	25	29	22	28	4.3%	1.70 [0.43, 6.84]
Yan HX 2012[37]	22	32	21	34	8.9%	1.36 [0.49, 3.77]
Jia LQ 2003[38]	18	23	15	22	4.7%	1.68 [0.44, 6.39]
Han WL 2011[39]	28	31	25	30	3.4%	1.87 [0.40, 8.62]
Wen X 2010[44]	25	27	19	29	1.9%	6.58 [1.29, 33.62]
Wang YL 2007[45]	29	32	24	32	3.1%	3.22 [0.77, 13.50]
Ruan FX 2012[46]	32	32	30	32	0.6%	5.33 [0.25, 115.50]
Total (95% CI)		**712**		**708**	**100.0%**	**1.77 [1.33, 2.36]**
Total events	615		557			

Heterogeneity: Chi² = 8.15, df = 23 (P = 1.00); I² = 0%
Test for overall effect: Z = 3.91 (P < 0.0001)

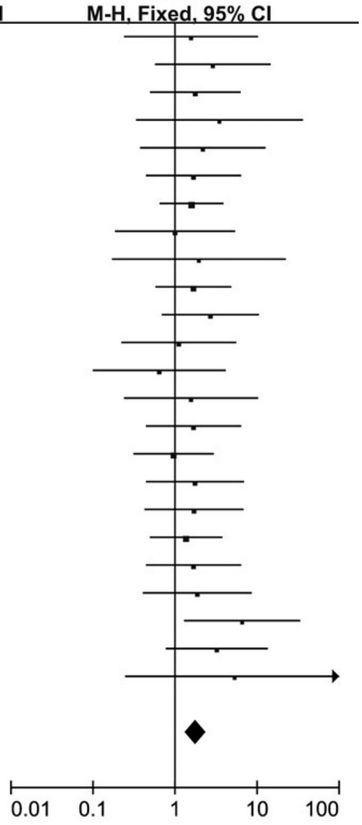

Figure 3 Clinical beneficial rate Meta-analysis

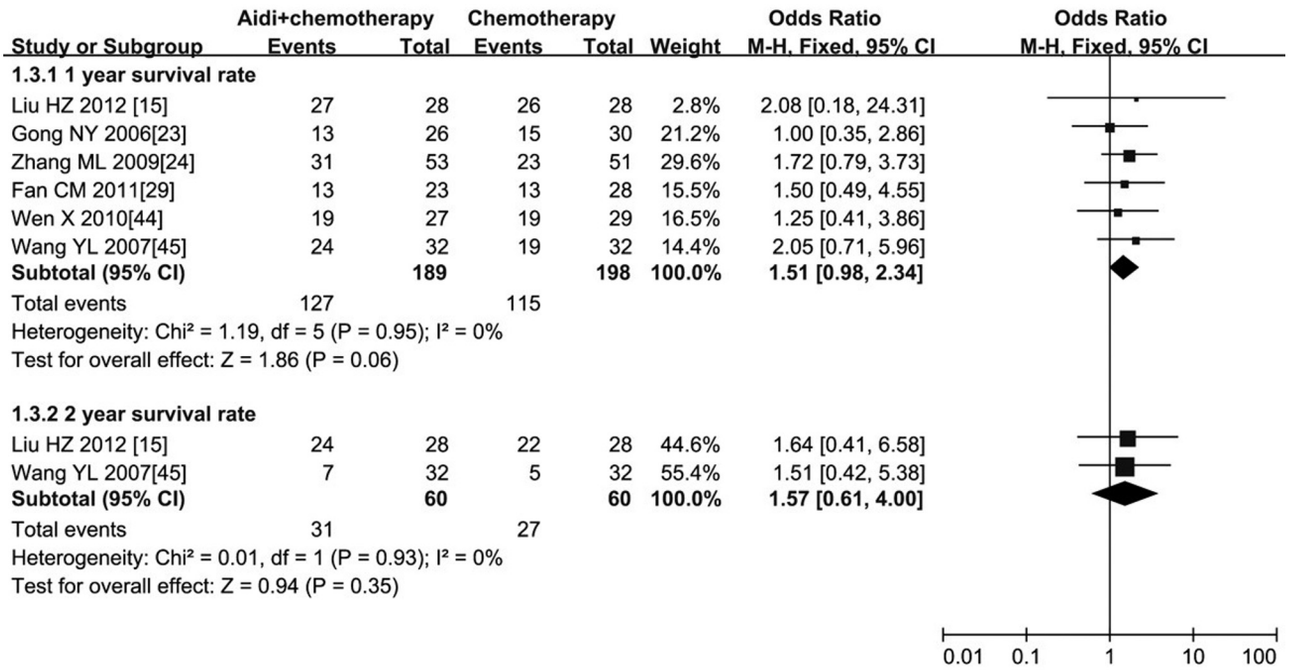

Figure 4 Survival rate Meta-analysis

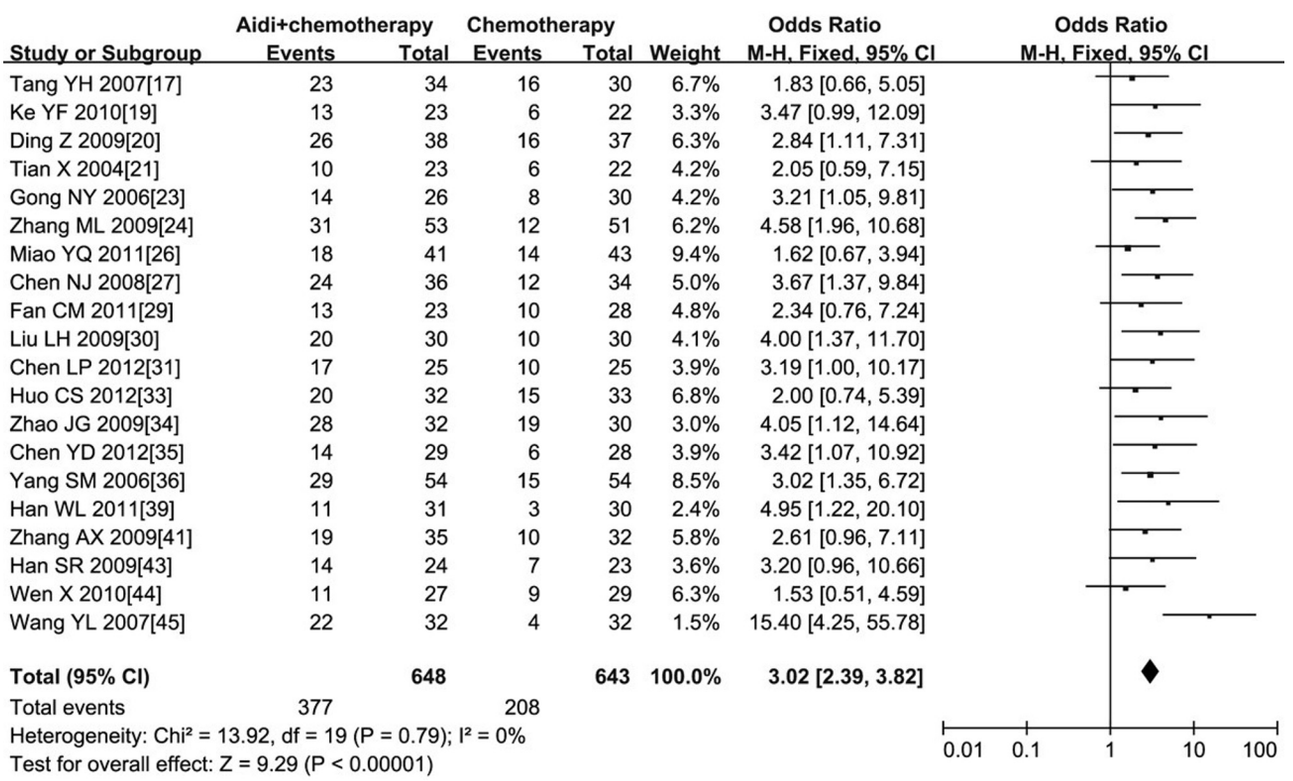

Figure 5 Quality of life Meta-analysis

bined with chemotherapy versus chemotherapy alone for GC. We found that Aidi injection combined with chemotherapy significantly improved effective rate, clinical beneficial rate, quality of life, immune function, and reduced some adverse events (nausea and vomiting, diarrhea, leukopenia (Ⅲ-Ⅳ), hemoglobin levels (Ⅲ-Ⅳ), thrombocytopenia (Ⅲ-Ⅳ), and damage to liver and kidney function). The injection combined with chemotherapy showed a trend towards increasing survival rate, but there was no significant difference between the two groups.

All included RCTs were randomized, but most of the 32 studies (90.63%) failed to describe the randomization methods. A statement such as "we randomly allocated" or "use a randomized design" was insufficient to confirm that the allocation sequence was genuinely randomized. One study,[17] which used paired admission number, is considered to have high risk of bias. One studyused a table of random numbers[29] and another drew lots[30] to generate randomized sequences, which areboth considered to have a low risk of bias. None of the studies reported whether there was blinding. This

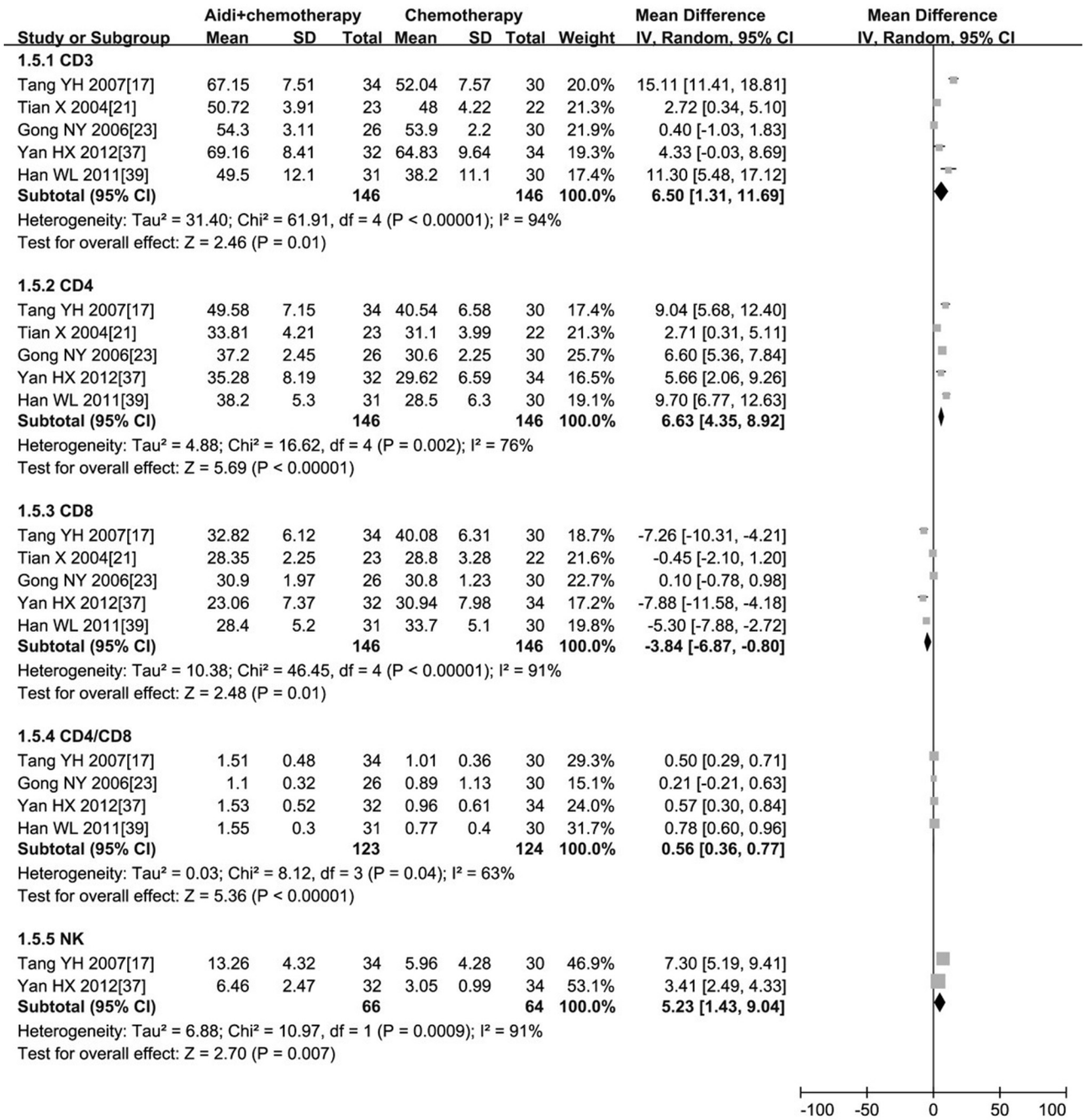

Figure 6 Nausea, vomiting, and diarrhea Meta-analysis

result could lead to implementation and measurement bias. Overall, the risk of bias in the included 32 studies was found to be medium. The funnel graph indicated a high likelihood of publication bias, which meansthat negative resultsare less likely to be published.

All studies included in our Meta-analysis were published in Chinese. We used a comprehensive search strategy and strived to reduce selection bias by searching PubMed, EMBASE, Cochrane Library, Science Citation Index Expanded, and the Chinese-foreign Conference Database. However, no studies published in English were found. Although we included 32 studies covering 1927 participants, only two studies included samples of more than 100 patients. More large-scale randomized double-blind control trials are needed to overcome methodological and reporting flaws.

There are some critical reporting flaws ofthe included studies.The methods of randomization were not described, and blinding was not reported. Therefore, the authenticity and reliability of the results of all included studies are affected.

Compared with chemotherapy alone, Aidi injection combined with chemotherapy could improve the effective rate; clinical beneficial rate; quality of life; immune function; and reducethe incidence of nausea and vomiting, diarrhea, leukopenia (Ⅲ-Ⅳ), hemoglobin decreases (Ⅲ-Ⅳ), thrombocytopenia (Ⅲ-Ⅳ), damage to the liver and kidney. Use of the CONSORT statement[47] for RCTs is recommended for stricter reporting of detailed information.

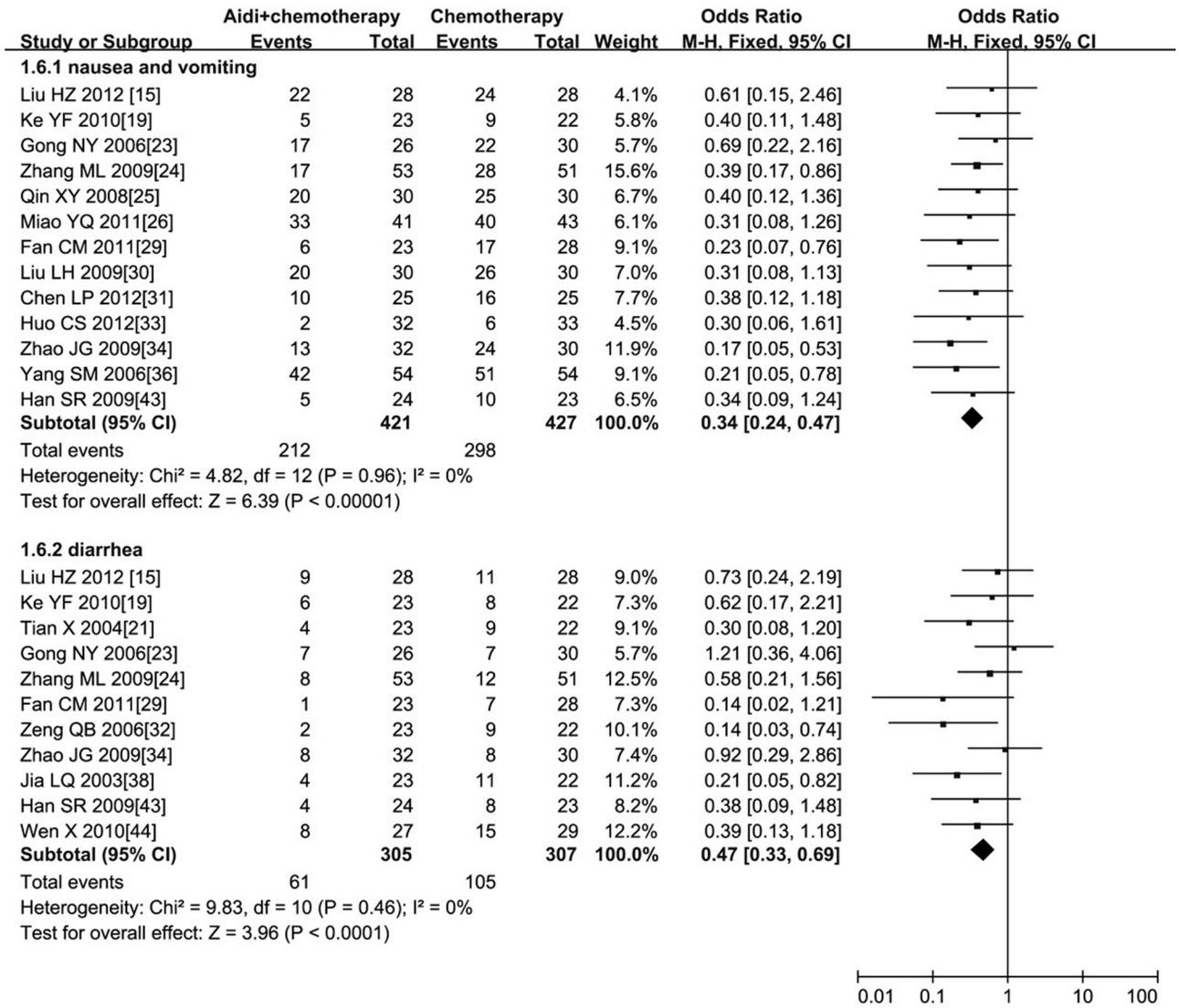

Figure 7 Leukopenia, hemoglobin decreases, and thrombocytopenia (Ⅲ-Ⅳ) Meta-analysis

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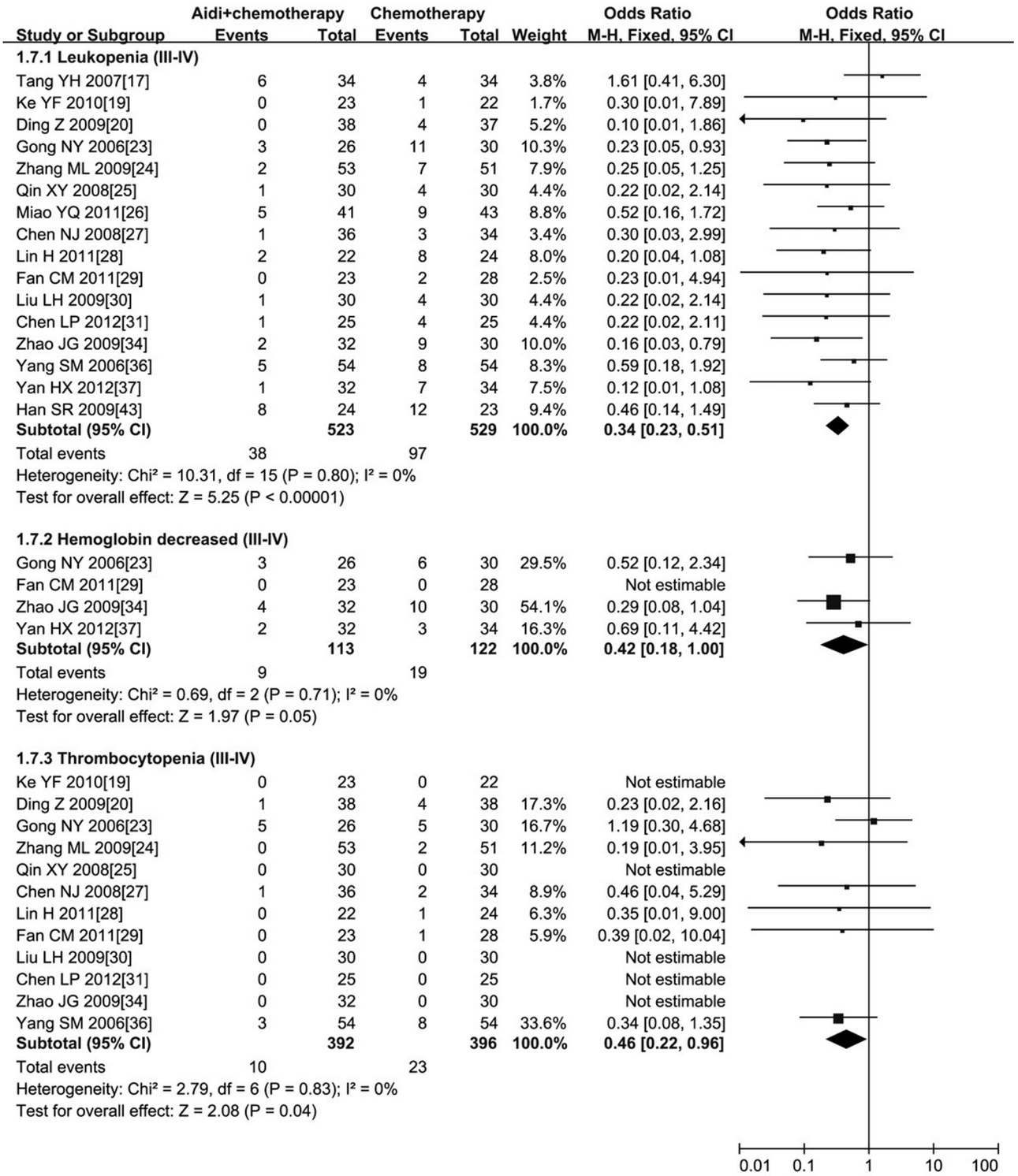

Figure 8 Damage to liver and kidney function Meta-analysis

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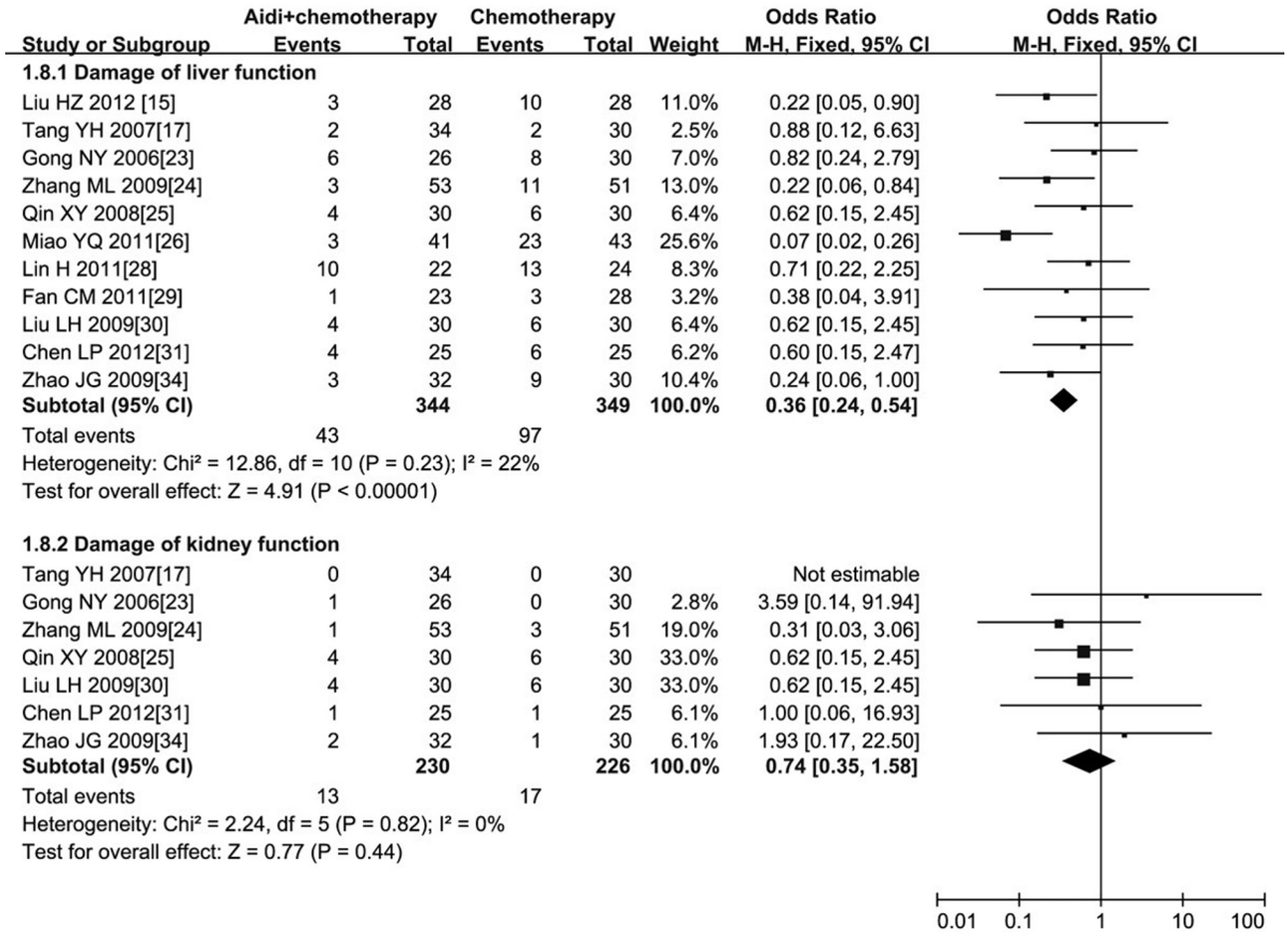

Figure 9 Immune function Meta-analysis

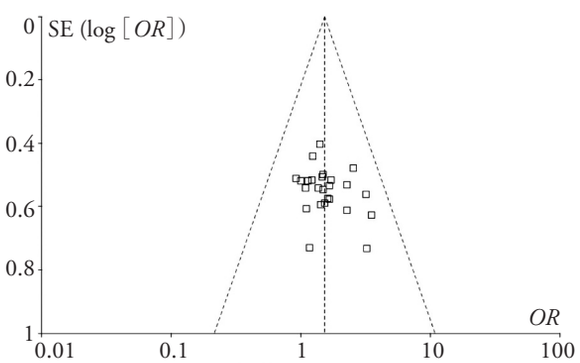

Figure 10 Funnel plot of effective rate

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